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#### Micronutrient deficiencies in the preterm neonate

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For any micronutrient there are daily intakes below which symptoms of deficiency are likely to occur, and above which symptoms of excess may occur. Within these extremes there is a range of intakes which, for most individuals, will be associated with good health, and which can be considered to be the daily requirement for the majority of individuals.

A useful distinction to make is between clinical deficiency and subclinical deficiency. For it to be possible to recognize or identify subclinical deficiency in an individual, it must be possible to relate some biochemical or physiological measurement to a range of normal values. Subclinical deficiency of a vitamin or a mineral can accordingly be identified by reference to such indicators as plasma levels; erythrocyte concentration; excretion of abnormal metabolites; or the activity of a micronutrient-dependent enzyme.

The biochemical reference values used to identify vitamin or mineral status in the premature infant are, in the most part, taken from normal values in infants and children, which are almost certainly inappropriate. For some micronutrients, such as Fe and vitamin E, there have been studies in premature infants relating clinical abnormalities with intakes and biochemical measurements of status, for which it is, therefore, possible to attach some functional significance (Younkin *et al.* 1971; Oski, 1985).

#### THE VULNERABILITY OF THE PRETERM INFANT

A number of factors associated with uterine life and postnatal care influence micronutrient status after birth. Table 1 summarizes the factors influencing the development of vitamin or mineral deficiency in the preterm infant.

#### DO DEFICIENCIES EXIST?

Clinical deficiencies of some vitamins and minerals do occur in infants born prematurely, and these are summarized in Table 2. It can be more difficult, though, to define and interpret biochemical evidence of poor micronutrient status using available threshold values. Subclinical deficiencies of many micronutrients do occur in prematurity, and as

Table 1. *Factors influencing the development of micronutrient deficiency in the premature infant*

<i>in utero</i>	Poor placental transfer, poor maternal status
Neonatally	Low tissue stores at birth, immaturity of absorption mechanisms, immaturity of metabolic pathways
Postnatal care	The use of: Vitamin-antagonistic drugs, phototherapy, high pO <sub>2</sub> Delayed introduction of feeds, loss of vitamins in the delivery system

Table 2. *Micronutrient deficiencies in preterm babies*

Micronutrient	Evidence	Clinical significance	Reference
Vitamin A	Low plasma retinol; high RBP response	Possible risk factor for BPD	Hustead <i>et al.</i> (1984)
Vitamin E	Low plasma tocopherol, increased erythrocyte fragility	Possible risk factor for BPD; haemolytic anaemia; neurological damage	Gross & Melhorn (1972)
Vitamin K	Hypothrombinaemia	Haemolytic anaemia	McNinch <i>et al.</i> (1983)
Riboflavin	High EGRAC	Impaired Fe absorption; altered GI function*	Lucas & Bates (1984)
Folic acid	Low plasma and erythrocyte cell folate	Macrocytic anaemia†	Ek <i>et al.</i> (1984); Ek (1985)
Fe	Low plasma ferritin	Microcytic, hypochromic anaemia†	Dallman (1974)
Cu	Low plasma Cu and caeruloplasmin	Splenomegaly, hepatomegaly, hypotonia, osteoporosis†	Al-Rashid & Spangler (1971); Manser <i>et al.</i> (1980)
Ca and P	Hypocalcaemia and hypophosphataemia	Poor bone mineralization; fractures	Hall <i>et al.</i> (1989)
Zn	Low plasma Zn	Acro-oral skin lesions, impaired brain function†	Sivasubramanian & Henkin (1978), Shaw (1979); Zimmerman <i>et al.</i> (1982)

RBP, retinol-binding protein; BPD, bronchopulmonary dysplasia; EGRAC, erythrocyte glutathione reductase (*EC* 1.6.4.2) activation coefficient; GI, gastrointestinal.

\* Not yet proven.

† Usually develops some weeks after birth.

the premature infant has a relatively poor capacity to adapt to altered metabolic circumstances such deficiencies should be taken to indicate a risk of metabolic disturbances.

Some consideration will now be given to some specific micronutrients which have received the most attention by workers in this field.

#### VITAMIN A

Despite the absence of clear-cut clinical symptoms of deficiency specific to vitamin A, a great deal of attention has been given to the requirement of the premature baby for this

vitamin. Evidence for deficiency includes low plasma retinol and retinol-binding protein. Retinol levels in the preterm baby or cord blood after birth fall into the range 0.26–1.08  $\mu\text{M}$ , compared with the conventional cut-off point for normality of 0.7  $\mu\text{M}$ , or the more stringent criterion of 0.35  $\mu\text{M}$  (Baker *et al.* 1977; Brandt *et al.* 1978; Montreewasuat & Olsen, 1979). Thus, some, but not all, premature babies are born with low circulating retinol. The low plasma retinol levels at birth are primarily a product of short gestation; analyses of fetal liver retinol stores show a doubling of liver retinol from 25 to 37 weeks gestation (Farrell *et al.* 1985). The limited information available suggests that the vitamin A status of the mother does not appear to have a direct influence on that of the newborn baby unless the mother is deficient in the vitamin. Large retinol supplements to the mother do not influence the status of the newborn baby unless the mother is malnourished (Montreewasuat & Olsen, 1979). The effects of postnatal life on vitamin A status in the preterm baby have not been properly evaluated, but the premature infant may face the combined disadvantages of low stores, a period of no vitamin intake at all, followed by a period of parenteral feeding, with a high loss of retinol in the delivery system (Hartline & Zachman, 1976; Shenai *et al.* 1981). Available information suggests that retinol levels after birth may remain low or fall, even when enteral or parenteral feeding is initiated. Our own findings show low levels of plasma retinol on the day of birth in premature babies, which remain low for some days thereafter, but increase as vitamin A is introduced into the diet. Of particular interest is the very close agreement observed between plasma retinol and calculated vitamin A intake.

What is the physiological significance of these findings? Particular interest has been shown in the possible contribution that low retinol levels at birth may make to chronic lung disease seen in these babies. Poor retinol status may compromise the efficiency of epithelial cell repair in lung tissue damaged by exposure to high partial pressure of  $\text{O}_2$ . There is some evidence for an association between low plasma retinol levels and the development of bronchopulmonary dysplasia (BPD) (Shenai *et al.* 1982; Hustead *et al.* 1984). Two intervention studies have been reported. Shenai *et al.* (1987) demonstrated a beneficial effect of supplements of 670  $\mu\text{g}$  retinol on alternate days on the incidence and severity of BPD. Pearson *et al.* (1992) failed to demonstrate a beneficial effect of a similar regimen but this result may reflect higher baseline vitamin A intakes in the study group. Current ESPGAN guidelines (ESPGAN Committee on Nutrition of the Preterm Infant, 1987) are that formulas should provide about 120–200  $\mu\text{g}/\text{kg}$  per d. The same committee, however, advocates supplements of up to 1000  $\mu\text{g}/\text{d}$  to babies fed on breast milk. This contrasts with the current reference nutrient intake for term babies which is 350  $\mu\text{g}/\text{d}$  (Department of Health, 1991).

#### VITAMIN E

Assessment of vitamin E status is most commonly made by the determination of plasma levels of  $\alpha$ -tocopherol, but the relationship between plasma levels and tissue levels is not clear. There is a marked influence of circulating lipids on plasma  $\alpha$ -tocopherol concentrations, but a detailed study of premature infants has suggested that expressing plasma  $\alpha$ -tocopherol relative to circulating lipid may be no more informative than plasma  $\alpha$ -tocopherol in assessing vitamin E status in this group (Horwitt *et al.* 1972; Gutcher *et al.* 1984). Plasma  $\alpha$ -tocopherol values in preterm babies at birth are reported to be in the range 0.7–10.7  $\mu\text{M}$  which is similar to the range reported for term babies, but very much lower than the normal range for adults (Tanaka *et al.* 1988; Lindeman *et al.* 1989).

Low plasma  $\alpha$ -tocopherol is associated with high rates of peroxide-induced erythrocyte haemolysis. There is limited information regarding the progress of vitamin E status after birth. Our own findings indicate that plasma  $\alpha$ -tocopherol levels fluctuate around a low mean value for some days after birth, but increase thereafter, sometimes quite dramatically, as feeds change to include lipid and fat-soluble vitamins.

Poor vitamin E status seen in premature babies has been ascribed to a number of factors including low tissue levels at birth, poor placental transfer, relatively poor absorption of vitamin E in the smallest premature infants, and the withholding of lipid feeds for several days after birth (Gross & Melhorn, 1972; Leonard *et al.* 1972). Persistently low levels of vitamin E in the preterm infant are associated with an increased likelihood of haemolytic anaemia (Farrell, 1980). Considerable interest has been shown in the antioxidant capacity of  $\alpha$ -tocopherol with regard to the possible preventative or ameliorative effects on the incidence of disease of the premature neonate, particularly BPD, intraventricular haemorrhage and retrolental fibroplasia. A plethora of studies have investigated the therapeutic value of supplementary vitamin E. Some of the results in this field are encouraging, but concern is warranted over serious clinical complications that have arisen with the use of very high doses of vitamin E (Mino, 1989). Current ESPGAN Committee on Nutrition of the Preterm Infant (1987) guidelines for infant formulas are for an  $\alpha$ -tocopherol:PUFA value of  $>0.9$  mg/g and an  $\alpha$ -tocopherol content of  $>1.43$  mg/MJ ( $>6$  mg/1000 kcal), which would provide about 0.78 mg/kg per d.

## VITAMIN D, CALCIUM AND PHOSPHORUS

### *Vitamin D*

Although dietary vitamin D is important after birth in order to achieve or maintain plasma biochemistry (Robinson *et al.* 1981), there is no convincing evidence that bone disease in the premature baby is primarily due to a deficiency of vitamin D, and no obvious benefits are associated with high intakes of vitamin D.

The balance of evidence indicates that preterm babies are able to metabolize vitamin D and to modulate Ca homeostasis from an early age. ESPGAN Committee on Nutrition of the Preterm Infant (1987) guidelines are for total intakes of vitamin D of 20–40  $\mu$ g/d. It is further recommended that any supplements should fall to 10  $\mu$ g/d once the baby reaches term or when the baby leaves hospital.

### *Calcium and phosphorus*

The pathogenesis of skeletal lesions is invariably multifactorial. Both hypocalcaemia and hypophosphataemia occur in the premature infant, and poor bone mineralization is indicative of inappropriate intakes of Ca and P. Ca and P deficiency may occur in the neonate through a number of mechanisms. Rates of Ca and P accretion increase significantly in the last trimester of pregnancy (Shaw, 1973) and there is a practical limit to the concentration of Ca and P achievable in infant formulas. Despite this there is ample evidence to show that preterm babies fed on infant formulas show improved bone mineralization (Steichen *et al.* 1980; Greer *et al.* 1982) in comparison with babies receiving human milk only, or unsupplemented formulas. The most important factor in the aetiology of 'rickets of prematurity' appears to be a low P intake or an unbalanced

Ca:P value. Inadequate P intake leads to hypercalciuria and poor bone mineralization (Hall *et al.* 1989). Bone fractures accompany demineralization in severe forms of rickets.

ESPGAN Committee on Nutrition of the Preterm Infant (1987) recommend Ca intakes from formulas should fall in the range 70–170 mg/kg per d and P intakes in the range of 35–160 mg/kg per d. The Ca:P value should be maintained within the range 1.4–2.0.

#### WATER-SOLUBLE VITAMINS

The placental transfer of these vitamins occurs by active mechanisms up a concentration gradient. If nutrient intakes are inadequate in the mother, this will not necessarily be reflected in fetal accumulation of the nutrient unless severe depletion occurs.

##### *Vitamin C*

Vitamin C depletion severe enough to elicit scurvy has been described in premature babies, but the current practice of including the vitamin in infant formulas, as well as the daily administration of multivitamin supplements makes this likelihood extremely rare. In our experience, the plasma ascorbic acid concentrations in the premature baby at birth tend to be high, fall in the first week and can rise to levels of 300  $\mu\text{M}$ , far in excess of the normal adult range. Some very recent work (Wilson *et al.* 1992) suggests that very-low-birth weight babies have a much higher oxidized:reduced form of ascorbic acid. It remains to be seen whether this represents a reduced antioxidant potential compared with that in adults.

##### *Riboflavin*

Angular stomatitis and seborrheic dermatitis, associated with riboflavin deficiency in adults, have not been reported in premature infants. Biochemical ariboflavinosis has been reported in unsupplemented babies, and this is exacerbated by phototherapy (Sisson, 1987). The functional significance of this is not clear, but riboflavin has been implicated in the maintenance of normal intestinal function, which is of particular importance to the neonate (Powers *et al.* 1991, 1993).

##### *Folic acid*

Controversy still surrounds the need for folic acid supplements during pregnancy and the optimum regimen for the neonate is not yet clear. In the period following birth, plasma and erythrocyte folate levels fall; if levels are allowed to remain low for an extended period, megaloblastic changes may occur in the bone marrow, and macrocytic anaemia ensue. Some recent work indicates that daily supplements in the range of 0.05–0.2 mg folate are adequate, and may be preferable to the practice of giving much larger doses (Fuller *et al.* 1992).

#### MINERALS

Clinical deficiencies of Cu, Fe, Zn, Ca and P in premature babies have all been documented (Table 2). Assessment of mineral status in premature infants, and interpret-

ation of results has been hampered by the lack of appropriate methodology. With the increased availability of mass spectrometry and other techniques, more useful information is emerging in this area.

#### SUMMARY

The nutrition of the premature infant poses a critically important challenge to clinicians. Premature infants are a heterogeneous group; maternal status, gestational age, drug intake, respiratory distress, phototherapy, and infection all conspire to make it extremely unlikely that a recommendation for daily intakes will satisfactorily encompass all babies. Clinical and subclinical deficiencies evidently do occur, and the impact of nutrient imbalance may have serious implications for outcome. If advances in clinical practice mean enhanced survival rates of babies of very small gestational age, then it is of vital importance that we work to establish the most appropriate regimens for vitamin and mineral intakes in this group.

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